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Original article

Placental growth factor and placental perfusion

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Proceedings

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Abstract

Placental Growth Factor (PlGF) is a very important angiogenic protein secreted by the placenta, necessary for the proper functioning of the endothelial cells during pregnancy. In normal pregnancies, PlGF plasma circulating levels increase up to the 32nd week of pregnancy, and then decrease until the end of pregnancy. Low PlGF plasma levels are a marker of preeclampsia and of placental function deficiency. The aim of our study was to evaluate whether a deficiency of placenta function, diagnosed through the PlGF assay, could be a cause of preterm delivery without known causes. The PlGF levels were measured in plasma samples collected by 250 pregnant women (20-35 weeks of pregnancy). In our study, PlGF levels were significantly lower than cut off values in all women with preterm delivery without known causes.

Keywords

Placental growth factor, placental function, preterm delivery, placental perfusion, neonatal outcomes.

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Introduction

Placental Growth Factor (PlGF) is an angiogenic protein secreted by the placenta [1]. It is well known by *in vitro* studies that hypoxia regulates the expression of PlGF in placental tissues [2]. Together with the Vascular Endothelial Growth Factor (VEGF), PlGF has been shown to be necessary for the proper functioning of the endothelial cells during pregnancy. Oxygen is the main regulator of the balance between PlGF and VEGF functions [3]. The expression of PlGF is stimulated by high PO_2 and reduced by a low PO_2, while the VEGF and its receptors are regulated by a low PO_2 [4, 5]. In normal pregnancies plasma circulating levels of PlGF increase up to the 32nd week of pregnancy, and then decrease until the end of pregnancy [1]. In preeclampsia, as a response to oxidative stress and inflammation, the placenta increases the release of soluble receptor for PlGF, fms-like tyrosine-kinase-1 (sFlt1). Thus, the circulating levels of free PlGF are lower in pregnant women with preeclampsia [6] and in those with uteroplacental ischemia [7]. Low PlGF levels are considered a marker of preeclampsia [8] and of a deficiency of placental function [9]. Previous studies of ours showed that low PlGF is associated with pathological features of placenta, such as anatomic signs of chronic hypoxia [10]. Although in 62% of cases it is possible to recognize the cause of premature labor, in the remaining 38% the causes are unknown [11].

The aim of our study was to evaluate whether a deficiency of placenta function, diagnosed through the PlGF assay, could be a cause of preterm delivery without known causes.

Subjects and methods

The PlGF levels were measured in plasma samples collected by 250 pregnant women between 20-35 weeks of pregnancy, recruited at the Department of Obstetrics Gynecology, University of Cagliari, during hospitalization or during the test for the diagnosis of gestational diabetes. All subjects gave their informed consent to the study, which was approved by Ethical Committee of the Department. The quantitative determination of PlGF was performed with the instrument Triage® Meter (Alere™) by fluorescence immunoassay on plasma samples obtained from blood collected in tubes containing EDTA anticoagulant. Chi-square test was used for statistical analysis. A hundred and twenty-three placentas were sent to Pathology Department for histologic examination. Later, the type of delivery, neonatal weight and outcomes were also assessed.

Results

In 201 women plasma PlGF levels were in the normal range for gestational age (defined as "control group"), whereas in the remaining 49 the PlGF levels showed to be lower than those expected for the gestational age (defined as "study group"). Of the 250 pregnancies examined, the histological examination of the placenta was performed in 123 cases. In the control group, 5 cases of hypoxic placenta (5.5%) were diagnosed. In the study group, 15 cases of hypoxic placenta out of the 33 examined (45.4%) were diagnosed. Between the two groups, the percentage of hypoxic placentas was significantly higher (chi-square, $p < 0.0001$) in the study group. In the control group, cases of placenta with maternal malperfusion were not reported. In the study group, 5 cases of placenta with maternal malperfusion (15.1%) were diagnosed.

Between the two groups, the percentage of placentas with maternal malperfusion was significantly higher (chi-square, $p = 0.0002$) in the study group. In the control group, 7 infants (3.3%) small for gestational age (SGA) were observed. In the study group, 16 infants (30.7%) SGA were found. Between the two groups, the percentage of SGA fetuses was significantly higher (chi-square, $p < 0.0001$) in the study group. In the control group, 25 (12.5%) preterm deliveries were recorded, including 2 early preterm and 23 late preterm. In the study group, 17 (34.7%) preterm births were reported, including 4 early preterm with severe abnormalities of the placenta (maternal malperfusion), 6 late preterm infants with hypoxic placenta, 4 late preterm without placental hypoxia and 3 late preterm with not rated microscopic examination of the placenta.

In the study group in which the placenta was examined (35 newborns, 2 sets of twins), 10 (29%) were admitted to Neonatal Intensive Care Unit (NICU) for respiratory problems (asphyxia, MAP, RDS), 2 of them died and 8 survived without morbility. Seven newborns (20%) were admitted to Puericulture Institute for infectious diseases

and eating disorders, all were discharged without morbility.

In the control group in which the placenta was examined (93 newborns, 3 pairs of twins), 6 (6.5%) were transferred to NICU, including 5 for respiratory diseases (asphyxia, MAP, RDS) and 1 for Noonan syndrome. Thirteen infants (14%) were admitted to Puericulture Institute for eating disorders, infectious diseases, and weight loss, all were discharged without morbility. No infant in the control group died.

Discussion

Placental Growth Factor can be considered a marker of placental function. The aim of this study was to evaluate if a possible cause of preterm delivery could be a deficiency in placental perfusion and its function. Recently, it has been suggested that the values of PlGF are lower than those of controls at least 5 weeks before the onset of true preterm labor [12]. Bastek et al. [13] show that in preterm delivery low PlGF levels are associated with high levels of a marker of inflammation, such as the C-Reactive Protein (hsCRP), suggesting an interplay between inflammation and placental dysfunction in the pathogenesis of preterm labor. In our study, PlGF levels were significantly lower than cut-off values in all women with preterm delivery without known causes. This agrees with our hypothesis that a placental dysfunction could be a cause of preterm labor and delivery, as suggested by previous authors [12, 13].

These preliminary data suggest, in agreement with the literature, that PlGF is a good index of placental function, especially of placental perfusion. In cases with values below the cut-off PlGF for gestational age, histology of the placenta showed clear alterations, in particular chronic hypoxia, confirming the correlation between low levels of PlGF and anatomical and functional alterations in perfusion of the placenta.

If we consider that the average time, in weeks, between the recruitment of patients in the study, and therefore the detection of PlGF levels below the cut-off for gestational age, and the performance of preterm birth is 2.9 weeks, we can adfirm that PlGF has a reasonable predictive value about the timing of delivery.

The inability to improve the framework of placental perfusion at gestational age in which it was executed our study prevents us from using the assay as a screening test. However, an evaluation of this marker in earlier gestational ages, in particular at the end of the first quarter, associated with other parameters, such as the Doppler flowmetry of the uterine arteries, can be effectively used to improve the outcome of pregnancy and fetal development, with the aim of improving the placentation and placental perfusion itself, thus reducing the risk of preterm delivery, preeclampsia, IUGR.

The relationship between PlGF values and placental function can give a prediction on baby's outcome immediately after the delivery. Our data show that in the study group there are a higher percentage of newborns requiring the admission in NICU and Neonatal Pathology than in control group.

Declaration of interest

The Authors declare that there is no conflict of interest.

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